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EDITORIAL COMMENT

Can Body Fat Cause Aortic Stenosis?

Lessons From Genetics*

Cécile Oury, PhD, Nathalie Donis, MSc, Patrick Marechal, MD

Degenerative aortic stenosis (AS) is the most common valvular heart disease in industrialized countries, with a prevalence reaching ≤13% above 75 years of age. Due to population ageing, a steadily increase of AS prevalence is foreseen in the years to come. AS is a progressive and insidious disease that remains asymptomatic for a very long time. Long-lasting valve dysfunction results in left ventricle remodeling and cardiac impairments that are often irreversible at symptom onset. Hence, AS is a disease of the valve and of the myocardium, resulting in inevitable fatal outcome if left untreated. There are currently no pharmacotherapies that can halt or delay AS progression, the only treatment being aortic valve replacement (AVR) (1,2). It is therefore crucial to identify risk factors of the disease to adopt optimal management measures and reduce AS burden. A recent study performed on 71,817 individuals from the Cohort of Swedish Men and the Swedish Mammography Cohort indicated that increases of body mass index (BMI) and waist circumference were associated with the incidence of aortic stenosis (3). This study was the first strong indication that obesity might represent a major risk factor of AS. This observation was likely to have a major impact on human health. Indeed, according to the most recent global estimates by the World Health Organization, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016, and these numbers are expected to rise. Along with ageing, obesity could thus be considered a leading cause of increased AS prevalence. Obesity, defined as a BMI ≥30, globally develops due to increased intake of fat-rich, energy-dense foods and physical inactivity related to environmental and societal habits (**Figure 1**). On top of these modifiable factors, genetics determines the susceptibility of individuals to become obese. Largescale studies identified >125 common gene loci associated with different measures of obesity (4). The analysis of these variants in the general population can provide important information in regard to the existence of causal relationship between phenotypic traits, i.e., obesity and the risk of diseases. By applying so-called Mendelian randomization technique, it is indeed possible to examine the causal effect of obesity on AS by measured variation in genes that have been

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associated with obesity. Kaltoft et al. (5) are to be commended on their carefully conducted Mendelian randomization study, in this issue of the *Journal*, exploring the association of genetically determined obesity with risk of AS. A total of 108,211 individuals from the Copenhagen General Population Study were included in their study. The incidence of AS in this population was 982, and 409 AVR, during a median follow-up of 8.7 years. The investigators nicely demonstrated that individuals who were genetically susceptible to become obese, based on interrogation of the 5 top common genetic variants that have been associated with BMI (6), had higher risk of AS and AVR. Individuals were categorized by defining unweighted allele scores for BMI so that the investigators could show that individuals who were genetically more likely to be obese had an increased hazard ratio for AS. In addition to the genetic analysis, Kaltoft et al. (5) also measured BMI and waist-hip ratio (WHR) at inclusion. It was found that

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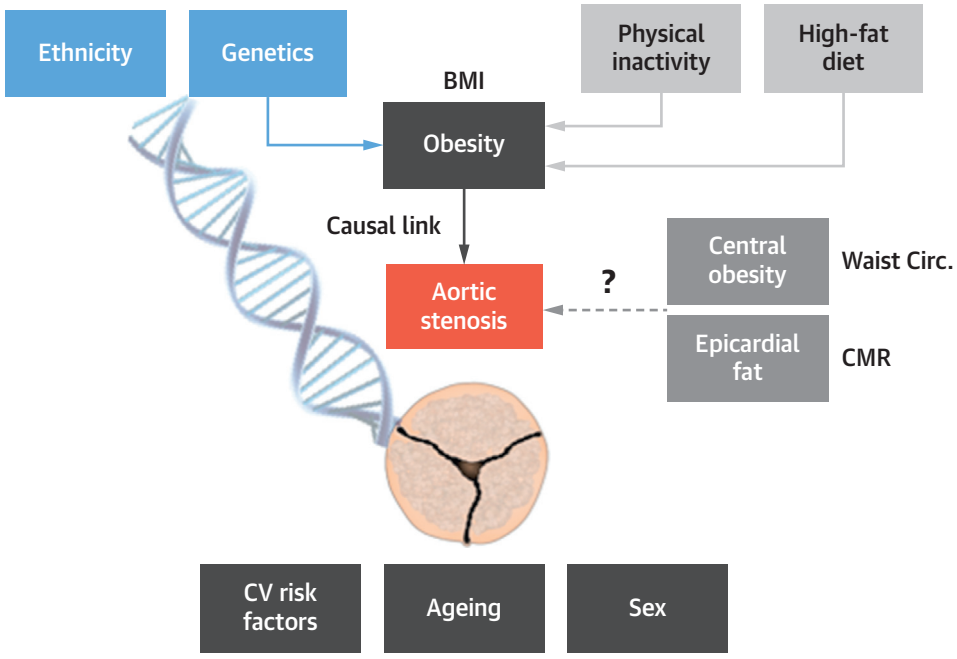
FIGURE 1 Overall Obesity as a Causal Risk Factor of AS



Genetic variants associated with obesity are associated with aortic stenosis, supporting the existence of a causal link between obesity and this disease. AS = aortic stenosis; BMI = body mass index; Circ. = circumference; CV = cardiovascular; CMR = cardiac magnetic resonance.

elevated BMI above 18.5 to 24.9 kg/m^2 or BMI increment of 1 kg/m^2 increased the causal risk ratios for aortic valve stenosis and replacement. A similar observation was made for WHR increases. It was therefore concluded that obesity was, observationally on the basis of BMI and WHR and causally on the basis of BMI genetics, associated with higher risk of AS and AVR.

A major limitation of Mendelian randomization relates to possible pleiotropic effects of the genetic variants used, i.e., single genetic variants can affect multiple phenotypic traits, which means that this approach may not necessarily provide a proof of causality (7). In the study by Kaltoft et al. (5), the use of allele scoring contributes to overcome this potential bias, which greatly strengthens their findings.

Recently, Mendelian randomization has contributed to our understanding of how lipid biology relates to cardiovascular risk (8,9). Besides, thanks to comprehensive largescale exome sequencing, novel low-frequency or rare (minor allele frequency <5%) coding variants, with relatively larger effects than common (minor allele frequency >5%) noncoding variants (10), are being discovered, highlighting potential causal genes underlying previously identified body-fat distribution loci (4). Such discoveries represent a major advance in our understanding of the biology and genetic architecture of central obesity. Whether central obesity is genetically associated with AS or AVR remains to be determined. Exploiting these new findings in Mendelian randomization studies may help in defining the association of central obesity with AS risk and understanding how lipid imbalance relates to AS risk, thereby providing new insights into AS etiology. Further, the identification of causal gene variants of body-fat distribution that would be associated with AS could reveal potential new therapeutic targets for preventive interventions. In addition to abdominal visceral fat, it would be interesting to assess the genetic association of epicardial fat, a visceral fat deposit located between the heart and the pericardium, with AS or AVR. Indeed, it has recently been reported that the epicardial fat volume, obtained by cardiac magnetic resonance imaging, may predict AS outcome (11), and unique gene loci appeared to be associated with pericardial fat (12).

In addition to well-known and presently demonstrated causal effects of increased BMI on cardiovascular and AS risk, raised BMI is also a risk factor for diabetes. There is evidence that type 2 diabetes mellitus predisposes to degenerative AS and

contributes to faster progression of AS. Moreover, diabetes is an independent determinant of cardiovascular mortality in patients with severe AS (13). We can then assume that studying the association of genetic variants related to combined raised BMI and diabetes mellitus with lifetime AS risk could be even more powerful than studies of isolated phenotypic traits. We believe that cross-trait association Mendelian randomization studies could highlight novel features underpinning patient's valvulometabolic and AS risk.

The princeps study of Kaltoft et al. (5) will likely be the basis for other studies intended to refine the causal link between body fat and AS risk in populations of various genetic ancestries.

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